REMARKS

The claims have been amended for clarification, in response to the criticisms set forth by the Office, and to more clearly distinguish the cited documents. Applicant appreciates the careful consideration of claim wording provided by the Office and believes that the amended claims are responsive. New claims 21 and 22 are similar to pending claims 15 and 16 but depend from claim 17. New claims 23-25, which require determination of the presence, absence or level of the signal transduction proteins at at least three locations are supported on page 11 of the specification, lines 1-2. New claims 26-28, which require that the localization pattern or profile be observed microscopically are supported in the specification, for example, on page 9, beginning at ling 25, on page 6, beginning at line 25, in claim 11 as originally filed, and throughout the specification. Support for new claims 29-31 which require observing the localization pattern or profile in fixed cells is supported in the specification on page 10, for example, lines 20-24. As kindly suggested by Examiner Lankford, "potentially" has been inserted into claims 17 and 19, as short of clinical trials, no protocol or compound can be 100% certain to be effective in treating a disease or condition. (Indeed, with respect to any individual, there is no 100% certainty even after such clinical trials.) No new matter has been added and entry of the amendment is respectfully requested.

Formal Rejections

A number of formal rejections were made under 35 U.S.C. § 112, paragraph 2. It is believed that the amendment to the claims is responsive to these rejections.

With respect to claim 14, because the Office is correct that toxicity is dependent on concentration, the claim has been clarified to specify that the toxic compound is supplied at a

concentration that is toxic. The Office is correct that the word "toxin" refers to the "toxic compound" in the preamble; "toxin" has been changed to "toxic compound" throughout.

Claim 14 has further been amended to obviate the rejection for asserted incompleteness. The preamble has been changed to read on "identifying" an antidote as the Office kindly recognizes is taught by the present application.

In claim 17, the word "similarity" no longer appears. The comparisons to be made have to do with generating patterns that resemble those that are desirable as compared to those that are undesirable. Applicant notes with appreciation that the characterization in claim 14 of a pattern "more closely resembling that under normal conditions" has not been criticized, and it is believed that this phrase is clear. Claim 17 has been amended to use this apparently satisfactory terminology.

Similarly, in claim 19, the word "similar" was again objected to. This, again, has been changed to what is apparently a more acceptable terminology. It is indeed believed that one of ordinary skill would understand how to recognize whether a test pattern more closely resembles one of two comparative patterns without further instruction. This was discussed at the interview, and it appeared agreeable that further delineation was not necessary.

In view of the amendments to the claims, the formal rejections may properly be withdrawn.

The Art Rejections

All claims were rejected as assertedly anticipated by Ping, *et al., Circ. Res.* (1999) 84:587-604 (Ping). The characterization of Ping made by the Office appears to applicant to be accurate. Ping indeed teaches observing whether various forms of signal transduction proteins are present in the cytosol or in the particulate fraction of cells. Changes are observed when certain compounds are administered to the subjects of the study; in one case, inhibitors of the compounds

administered were also provided to discern the effect of the inhibitor on the distribution of one of the PKC isozymes.

Ping teaches the three-way comparisons required by each of the independent claims only minimally – it is only in the single instance of adding an inhibitor along with a compound that provides the NO stimulus that there are three different distributions obtained.

The claims are presently proposed, however, distinguish Ping even more clearly than the claims as previously presented. In each of the independent claims, one of three stipulations must be met. None of them is met by Ping.

The first stipulation is that at least three locations in the cells be evaluated; Ping does not meet this limitation because the determinations are made simply of the distribution of a PKC isozyme between the cytosol and particulate fraction. The second alternative stipulation, that the observing of the localization pattern be done microscopically, is not met either; in Ping, observation is made by simply Western blot. Similarly, the third possible stipulation is not met – fixed cells are not observed, rather homogenates are created to obtain the cytosolic and particulate fractions.

Thus, all of the independent claims clearly distinguish Ping, which neither discloses nor suggests any of these limitations.

The pending claims were also rejected as assertedly anticipated by Brick-Ghannam, *et al.*, *J. Biol. Chem.* (1991) 266:24160-24715. Although Brick-Ghannam measure the activity of PKC both in the cytosol and the membrane fraction, there is no alteration of the localization pattern due to the presence of HLA class II antibodies. As stated, for example, on page 24173, "these data propose a new approach to the concept of PKC activation and suggest that this enzyme can be activated without being translocated." This is further stated in the abstract, "unlike TPA, no

translocation of cytosolic PKC was observed at any time following exposure to the anti-HLA class II antibodies." Thus, there would be no differing localization patterns in the presence and absence of HLA class II antibodies for comparison to any other profiles to determine whether a third profile more resembles one or the other – the profiles are the same. Brick-Ghannam do test the effect of certain compounds on the activation of PKC, but do not report on any effect of these compounds, such as actinomycin D, on a localization profile. Accordingly, although Brick-Ghannam test the effect of certain compounds on PKC activity, the article is silent on any effect on the localization pattern of signal transduction proteins and indeed, the localization patterns, both in the presence and absence of the HLA class II antibodies, are the same. Accordingly, Brick-Ghannam does not anticipate the invention as claimed.

As was the case with Ping, Brick-Ghannam clearly do not suggest the limitations of claims 23-31 as the localization patterns are determined macroscopically on cellular homogenates, not on fixed cells or microscopically.

Accordingly, the art rejections may properly be withdrawn.

Double-Patenting

Although the present application is a divisional, in order to preempt any possible double-patenting issues that might arise because of amendments to the claims in the present application, a terminal disclaimer with respect to the parent application which issued as U.S. 6,673,554 is enclosed.

CONCLUSION

The claims has been amended for clarity, and it has been demonstrated that neither cited document suggests the invention as now claimed. Applicant greatly appreciates the assistance of Examiners Yang, Gabel, and Lankford in designing claims that clearly distinguish the cited documents. Neither document includes any suggestion of any stipulation as required in claims 14, 17 and 19. Accordingly, it is believed that all pending claims, claims 14-17, 19 and 21-31 are in position for allowance and passage of these claims to issue is respectfully requested. If minor issues remain that might be resolved by a telephone discussion, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 388512010410.

Respectfully submitted,

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Enclosures:

a terminal disclaimer with respect to the parent application which issued as U.S. 6,673,554 is enclosed.